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EXAMINER	
STOICA, ELLY GERALD	

ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/587,370	KELLEY ET AL.	
	Examiner	Art Unit	
	ELLY-GERALD STOICA	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-50* is/are pending in the application.

4a) Of the above claim(s) *1-7, 12, 14, 16, 18, 19, 30-32, 35-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-11,13, 15,17,20-29,33 and 34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *07/26/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Inventions of Group II (claims 8-11, 13, 15, 17, 20-22 and the amended claims 23-29 and 33-34) and the species SEQ ID NO 18 in the reply filed on 07/31/2008 is acknowledged. As a result, claims 8-11, 13, 15, 17, 20-29 and 33-34 are currently examined.

Claim Objections

2. Claim 13 is objected to for containing non-elected subject matter. Appropriate correction is required.

Claim Rejections - 35 USC § 101

3. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 8-11, 13, 15, 17, 20-29 and 33-34 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims read on a product of nature in that the claimed polypeptide is not "isolated". In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. See *Diamond v. Chakrabarty,* 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by

insertion of "isolated" or "purified" as taught by page 40 of the specification. See MPEP 2105.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 8-11, 15, 17, 20-29 and 33-34 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the base claim (claim 8) recites amino acid X_{10} (see line 7). However, in the formula there is no amino acid designated X_{10} and the tenth position of the formula claimed is occupied by a unique amino acid, Leucine and thus it is not possible to establish the metes and bounds of the claims.

6. Claims 17, 20 and 21 are indefinite because in their recitations, reference is made to figure 5. Figure 5 consists actually of two sequences. Thus it is not clear which sequence is being referred to in the claim. Amending the claims to recite a specific SEQ ID NO:. would make the claims clearer.

Claims 17 and 20, 21 are also unclear because they recite a "mammalian" BCMA polypeptide, but the polypeptides in Figure 5 are only human. Thus, it is not clear if the specific amino acid positions referred to in the claims are indicative for all mammalian BCMA species/variants or just human.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 8-11, 15, 17, 20-29 and 33-34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a genus of peptides which have the functional limitation of binding BAFF. The structural limitations are either that the peptide is 85% identical with the cysteine rich domain (CRD) of "native" BCMA or is a peptide of formula:

C-X2-X3-X4-X5-X6-X7-D-X9-L-X11 –X12-X13-C-X 15-X16-C-X18-X19-X20-C-X22-X23-X24-X25-X26- X27-X28-X29-C-X31-X32-X33-C wherein X6 is selected from the group consisting of Y, A, D, S and F; wherein X11 is any amino acid residue except A; wherein X15 is any amino acid residue except A or K; wherein X18 is selected from the group consisting of Q, D and A; wherein X20 is selected from the group consisting of R, Y and A; wherein X2, X3, X4, X5, X7, X9, X10, X12, X13, X16, Xl9, X22, X23, X24, X25, X26, X27, X28, X29, X31, X32 and X33 are any amino acid except cysteine; and provided that the Formula II does not comprise the sequence CSQNEYFDSLLHACIPCQLRCS SNTPPLTCQRYC (which is the human BCMA TALL-1

binding motif) and also excludes the mouse BCMA by the limitations of X15 amino acid residue.

In regard to the independent claim 17 (and the dependent claims 20 and 21 the claim is interpreted as being drawn to any BCMA polypeptide (including different species, mutants and fragments) with one of the amino acid changes recited in the claims.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity or a formula which comprises 65% of the residues that might be any amino acid except Cysteine. With the exception of the cysteines and two other amino acids (D8 and L10) there are no constraints on the molecule. The instant specification identifies five functional peptides (SEQ ID NOs.: 13-18) which abide by the formula presented *supra* and bind BAFF. The specification does not identify the residues that are required in order to assure proper folding as well as functionality for BAFF binding. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus, because, until the Invention is reduced to

practice, a person of ordinary skill in the art cannot determine which of the numerous peptides would have the proper folding and have the functionality claimed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only the polypeptides consisting of the sequences of SEQ ID NOs 13-18 but not the full breadth of the claims meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the

written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

9. Claims 8-11, 15, 17, 20, 21, 22-29 and 33-34 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the peptides of SEQ ID NOs: 13-18, does not reasonably provide enablement for whole genus of peptides having the formula II or having 85% identity with the native BCMA amino acid sequence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

As presented above, the claims are drawn to a genus of peptides bind BAFF. The structural limitations are either that the peptide is 85% identical with the cysteine rich domain (CRD) of "native" BCMA or is a peptide of formula:

C-X2-X3-X4-X5-X6-X7-D-X9-L-X11 –X12-X13-C-X15-X16-C-X18-X19-X20-C-X22-X23-X24-X25-X26- X27-X28-X29-C-X31-X32-X33-C wherein X6 is selected from the group consisting of Y, A, D, S and F; wherein X11 is any amino acid residue except A; wherein Xl5 is any amino acid residue except A or K; wherein Xl8 is selected from the group consisting of Q, D and A; wherein X20 is selected from the group consisting of R, Y and A; wherein X2, X3, X4, X5, X7, X9, X10, X12, X13, X16, Xl9, X22, X23, X24, X25, X26, X27, X28, X29, X31, X32 and X33 are any amino acid except cysteine; and provided that the Formula II does not comprise the sequence CSQNEYFDSLLHACIPCQLRCS SNTPPLTCQRYC and also excludes the mouse BCMA by the limitations of X15 amino acid residue.

In regard to the independent claim 17 (and the dependent claims 20 and 21 the claim is interpreted as being drawn to any BCMA polypeptide (including different species, mutants and fragments) with one of the amino acid changes recited in the claims.

The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (.In re Colianni, 195 USPQ 150 (CCPA 1977)). Additionally, the courts have determined that "... where a statement is, on its face, contrary to generally accepted scientific principles", a rejection for failure to teach how to make and/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977) and have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986).

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

With the exception of the cysteines and two other amino acids (D8 and L10) there are no constraints on the molecule. The only sequences that are functional and disclosed are SEQ ID Nos. The instant specification identifies five functional peptides (SEQ ID NOs: 13-18) which abide by the formula presented *supra* and bind BAFF. The specification does not identify the residues that are required in order to assure proper folding as well as functionality for BAFF binding. As presented above, the specification only provides an enabling disclosure for SEQ ID NOs: 13-18, because, until the Invention is reduced to practice, a person of ordinary skill in the art cannot determine which of the numerous peptides would have the proper folding and have the functionality claimed. It would take a considerable amount of experimentation to obtain all the possible peptides as defined by the formula II (the number would be equal to 9.3 to the 29^{th} power), assuming that all the peptides theoretically possible could be obtained. And this large number does not include the other potentially large number of BCMA variants in claim 17.

While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, with the exception of peptides of SEQ ID NOs: 13-18 and the sequence from the wild type human BCMA, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250). As presented above, the specification

discloses only 7 peptides of an enormous number that form the genus claimed. Moreover, with regard to the "rules" for selecting the position and amino acids to be used in the respective positions, the followings are noted:

- Only conservative substitutions are permitted in the position x_{11} for BAFF binding (Specification, p.83, lines 18-19.
- No substitutions of x_{15} seem to be tolerated with respect to BAFF binding (Specification, p.83, lines 19-20, table 6 and figure 3).
- An alanine substitution does not seem tom be tolerated at x_{18} (figure 3 and table 6).

The disclosure in the specification is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Therefore, undue experimentation would be required of the skilled artisan to obtain and test all the peptides of the genus claimed. Due to the large quantity of experimentation necessary to generate the huge number of derivatives recited in the claims and possibly screen the same for activity; the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity; the absence of working examples directed to same; the complex nature of the invention; the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function; and the breadth of the claims which fail to recite any structural or functional limitations (except the native sequence of BCMA and SEQ ID NOs: 13-18) undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 8-10, 22, 25, 26, 28 and 33 and are rejected under 35 U.S.C. 102(b) as being anticipated by Browning et al. (U.S. Pub. No. 20020165156).

Browning et al. teach an immunoadhesin formed by inserting the cysteine rich domain of BAFF-receptor downstream of a murine IgG-kappa signal sequence and upstream of the Fc moiety of human IgG ([0088]). The sequence of the construct comprises the sequence CSQNEYFDSLLHACIPCQLRCSSNTPPLTCLHAC (within SEQ ID NO 3) and corresponds to all the limitations set forth in claim 8. The sequence is 91% identical with the sequence of a native BCMA. Also taught are pharmaceutical compositions comprising a BAFF-R polypeptide and a pharmaceutically acceptable excipient. It was also known in the art that peptides that contain Fc moieties have a longer half-life.

Thus Browning et al. anticipates the claims 8-10, 22, 25, 26, 28 and 33 of the instant Application.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

14. Claims 15 and 24 rejected under 35 U.S.C. 103(a) as being unpatentable over Browning et al. (U.S. Pub. No. 20020165156) in view of Feige et al. (U.S. Pat. No. 6,660,843).

The claims are drawn to a peptide which bind BAFF and comprises the sequence of the formula the: C-X2-X3-X4-X5-X6-X7-D-X9-L-X11 –X12-X13-C-X 15-X16-C-X18-X19-X20-C-X22-X23-X24-X25-X26- X27-X28-X29-C-X31-X32-X33-C wherein: X6 is selected from the group consisting of Y, A, D, S and F; X11 is any amino acid residue except A; X15 is any amino acid residue except A or K; X18 is selected from the group consisting of Q, D and A; X20 is selected from the group consisting of R, Y and A; X2, X3, X4, X5, X7, X9, X10, X12, X13, X16, Xl9, X22, X23, X24, X25, X26, X27, X28, X29, X31, X32 and X33 are any amino acid except cysteine; and provided that the Formula II does not comprise the sequence CSQNEYFDSLLHACIPCQLRCS SNTPPLTCQRYC. Specific limitations for the claims 15 and 24 are that the peptide further comprises the

sequence NSVKGT linked carboxy terminal to the thirty-fourth residue, or the polypeptide is attached to a non-proteinaceous polymer.

The teachings of Browning et al. were presented supra. Browning et al. is silent with regard to adding the sequence NSVKGT or adding a non-proteinaceous polymer.

The sequence NSVKGT is an integral part of the native BCMA (residues 47-52 in figure 5 of the specification). Based on the evidentiary reference of Liu et al. (Nature, 423, 49-56, 2003-cited by Applicant; figures 1,3-5), the portion of the BCMA molecule that contained the carboxi terminal C41 to which the NSVKGT is attached is not part of the interacting domain with BAFF (i.e. points away from the BAFF). The structure of the helix formed by residues 38-42 would be conserved since the N42 would be substituted by N47 (the N from the sequence NSVKGT).

Feige et al teach peptides that contain linkers comprising either C or K. The peptides can be PEGylated on these C or K residues. The linker was needed for introducing a PEG moiety far enough from a critical binding site in the peptide molecule. PEG is a known biocompatible polymer which is increasingly used as a covalent modifier to improve the pharmacokinetic profiles of peptide- and protein-based therapeutics ([0137]-[0138]).

It would have been obvious for a person of ordinary skill in the art at the time that the invention was made to add the linker NSVKGT to the peptide of Browning et al. for further PEGylation by using the teachings of Feige et al. with a reasonable expectation of success. This is because the linker would not have distorted the active site of the

molecule. The motivation for introducing the linker and the PEG is offered by Feige et al. which underscored the superior therapeutic qualities of PEGylated peptides.

15. Claim 27, 29, 33 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Browning et al. (U.S. Pub. No. 20020165156) in view of Ruben et al. (U.S. Pat. No. 6,969,519).

The claims are drawn to a BAFF binding polypeptide which is part of an antibody wherein the antibody is selected from the group consisting of an F (ab) antibody, F (ab') 2 antibody and a scFv antibody. Also the BAFF binding peptide may be attached to cytotoxic agent (a toxin, an antibiotic and a radioactive isotope). Finally, the peptide is part of a pharmaceutical composition further containing a chemotherapeutic agent.

The teachings of Browning et al were presented supra. They are silent about the antibody fragments or the cytotoxic agents linked to the peptide or added in a composition.

Ruben et al. teach about TR17, a novel member of the tumor necrosis factor family of receptors (also known as Tumor necrosis factor receptor superfamily 13B, TNFRSF13B, also synonym to TACI; see Uniprot entry No. O14836). One of the constructs taught is a TR17 peptide fused with an IgG. Further, obtaining fragment antibodies from the IgG molecule is considered routine in the art as indicated in col.44-45. Some of the fragment antibodies are conjugated to a therapeutic moiety such as a cytotoxin, e.g., a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion (col.73-74).

Ruben et al also taught compositions of the invention may be administered alone or in combination with other therapeutic agents, including but not limited to, chemotherapeutic agents or antibiotics.

It would have been obvious for a person of ordinary skill in the art at the time that the invention was made to have used the construct of Browning et al. according to the teachings of Ruben et al. with a reasonable expectation of success because both sets of constructs belong to the same superfamily of TNF receptors. The motivation to do so would have been offered by the vast array of therapeutical benefits underscored by Ruben et al. for their constructs, benefits and uses that could easily be transferred to the construct of Browning et al.

16. Claim 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over Browning et al. (U.S. Pub. No. 20020165156) in view of Ruben et al. (U.S. Pat. No. 6,969,519) and Oren et al. (Nature structural biology, 9, 288-292, 2002; cited by Applicant).

The claim is drawn to a peptide which bind BAFF and comprises the sequence of the formula the: C-X2-X3-X4-X5-X6-X7-D-X9-L-X11 –X12-X13-C-X 15-X16-C-X18-X19-X20-C-X22-X23-X24-X25-X26- X27-X28-X29-C-X31-X32-X33-C wherein: X6 is selected from the group consisting of Y, A, D, S and F; X11 is any amino acid residue except A; X15 is any amino acid residue except A or K; X18 is selected from the group consisting of Q, D and A; X20 is selected from the group consisting of R, Y and A; X2, X3, X4, X5, X7, X9, X10, X12, X13, X16, Xl9, X22, X23, X24, X25, X26, X27, X28, X29,

X31, X32 and X33 are any amino acid except cysteine; and provided that the Formula II does not comprise the sequence CSQNEYFDSLLHACIPCQLRCS SNTPPLTCQRYC and further comprises a leucine zipper.

The teachings of Browning et al. were presented above. They do not specifically suggest further adding a leucine zipper to the constructs.

Ruben et al. teaches about TR17, a novel member of the tumor necrosis factor family of receptors (also known as Tumor necrosis factor receptor superfamily 13B, TNFRSF13B, also synonym to TACI; see Uniprot entry No. O14836). Ruben et al. disclosed that certain members of the TNF family of proteins exist in trimeric form and the trimeric TR17 may offer the advantage of enhanced biological activity. Relative to this fact, Ruben et al. created multimers of the TR17 protein by using leucine zipper sequences (col.35, lines 11-41).

Oren et al. teaches the structure of BLyS (synonym for BAFF) to be a trimer with interaction sites (deep grooves) formed by pairs of monomers in the trimers (fig. 3).

It would have been obvious for a person of ordinary skill in the art at the time that the invention was made to have used the teachings of Ruben et al and add a leucine zipper to their construct to obtain a trimer with a reasonable expectation of success, because the constructs of Ruben et al. and Browning et al. were part of the same superfamily of TNF receptors. The motivation to do so would have been offered by Oren et al. which underscored the trimeric structure of BAFF and the chances for interacting with the BAFF binding protein would be greatly enhanced if the binding protein was also trimer.

17. Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al. (Nature, 423, 49-56, 2003-cited by Applicant).

The claim is drawn to a polypeptide that is a BCMA variant having an amino acid sequence derived from a mammalian BCMA polypeptide wherein at least one amino acid residue corresponding to the amino acid residue selected from the group Q10, E12, Y13, F14, I22, Q25 and R27 of the sequence provided in FIG. 5 of the specification.

Liu et al. teach the structure of the BCMA while interacting with TALL-1 (an alternative name for BAFF (p52, left column). In figure 3, Liu et al. delineates the conserved cysteines of the region involved in binding to BAFF as well as the residues involved in the ligand binding and, if substituted, would affect the binding. From the figure it can be inferred that substitutions at Q10 or E12 or F14 or Q25 are more likely than not to conserve the structure and the functionality of the peptide and possibly ensure a better contact with BAFF. The mutagenesis approach is a routine optimization practice in small peptide –protein interactions and is performed on large scale in pharmaceutical industry to obtain better interactions for either agonists or antagonists. Therefore, it would have been obvious to try to modify any of the residues mentioned (Q10, E12, F14 or Q25) to optimize the binding region of BCMA with a reasonable expectation of success as per the teachings of Liu et al. The changes would have implicated a relatively small number of sites (4) and the choice would have been from a

finite range (19 amino acids). A person of ordinary skill in the art is always motivated to pursue the known options within her or his technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

Conclusion

18. Claims 8-11, 13, 15, 17, 20-29 and 33-34 are not allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ELLY-GERALD STOICA whose telephone number is (571)272-9941. The examiner can normally be reached on 8:30-17:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Bridget E Bunner/

Primary Examiner, Art Unit 1647